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United States Patent [19][11] **Patent Number:** **5,271,961****Mathiowitz et al.**[45] **Date of Patent:** **Dec. 21, 1993**[54] **METHOD FOR PRODUCING PROTEIN MICROSPHERES**[75] Inventors: **Edith Mathiowitz**, Brookline;
Howard Bernstein, Cambridge; **Eric Morrel**, Needham; **Kirsten Schwaller**, Duxbury, all of Mass.[73] Assignee: **Alkermes Controlled Therapeutics, Inc.**, Cambridge, Mass.[21] Appl. No.: **902,505**[22] Filed: **Jun. 23, 1992**WO90/03123 4/1990 PCT Int'l Appl. .
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2224258A 5/1990 United Kingdom .**OTHER PUBLICATIONS**Sato et al., *Pharmaceutical Research*, vol. 5, No. 1, "Porous Biodegradable Microspheres . . ." (1988).Tice, et al., *J. Controlled Rel.* 2, 343-352 (1985).Suzuki, et al., *Pharm. Soc. Jap. Chem. Pharm. Bull.* 37 (4), 1051-1054 (1989).*Primary Examiner*—Robert L. Stoll*Assistant Examiner*—John M. Covert*Attorney, Agent, or Firm*—Kilpatrick & Cody**Related U.S. Application Data**

[63] Continuation of Ser. No. 557,551, Jul. 24, 1990, abandoned, which is a continuation-in-part of Ser. No. 432,785, Nov. 6, 1989, abandoned.

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A61K 9/52; A61K 9/54[52] U.S. Cl. **427/213.31**; 427/213.3;
427/213.36; 424/491; 424/499; 426/96[58] Field of Search 427/213.36, 213.3, 213.31;
264/4.6; 426/96; 424/491, 499[56] **References Cited****U.S. PATENT DOCUMENTS**3,092,553 6/1963 Fisher, Jr. et al. 264/4.4 X
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[57] **ABSTRACT**

Protein microspheres are formed by phase separation in a non-solvent followed by solvent removal. The preferred proteins are prolamines, such as zein, that are hydrophobic, biodegradable, and can be modified proteolytically or chemically to endow them with desirable properties, such as a selected degradation rate. Composite microspheres can be prepared from a mixture of proteins or a mixture of proteins with one or more bioerodible polymeric materials, such as polylactides. Protein coatings can also be made. Compounds are readily incorporated into the microspheres for subsequent release. The process does not involve agents which degrade most labile proteins. The microspheres have a range of sizes and multiple applications, including drug delivery and delayed release of pesticides, fertilizers, and agents for environmental cleanup. Selection of microsphere size in the range of less than five microns and mode of administration can be used to target the microparticles to the cells of the reticuloendothelial system, or to the mucosal membranes of the mouth or gastrointestinal tract. Larger implants formed from the microspheres can also be utilized, especially for agricultural applications.

20 Claims, 3 Drawing Sheets